

# Effects of ivermectin in dairy discharges on terrestrial and aquatic invertebrates

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# Effects of ivermectin in dairy discharges on terrestrial and aquatic invertebrates

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## ABSTRACT

Ivermectin (22,23-dihydroavermectin B<sub>1</sub>) is a broad-spectrum antiparasitic drug that was introduced for the control of parasitic worms and lice in sheep and cattle. This review summarises what is known about the impact of ivermectin in pastures and catchments and also on freshwater systems. Differing results have been obtained for the effects on decomposition of dung from ivermectin-treated cattle, although other experiments have shown adverse effects on growth of earthworms. There were likely to be risks to sediment-dwelling invertebrates where farmed salmon had been treated with ivermectin to control sea lice. In laboratory tests, freshwater fish appeared to have low sensitivity to ivermectin. In view of the lack of published information about environmental effects of use of avermectins and about endocrine-disrupting chemicals in detergents used in dairy operations, it is recommended that monitoring of dairy discharges for residues of such chemicals should be undertaken.

**Keywords:** dairy discharges, pollution, antiparasitic drugs, chemical residues, ivermectin, avermectins, endocrine-disrupting chemicals, invertebrates, freshwater systems.

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# 1. Introduction

The potential sources of pollutants originating from dairy shed operations include animal wastes, veterinary drugs, pesticides and other chemicals such as detergents and disinfectants. Overseas literature suggests that ivermectin could have adverse effects on dung- and soil-dwelling terrestrial invertebrates and on sediment-dwelling organisms inhabiting freshwater ecosystems. Chemical contaminants in dairy discharges could also aggravate the effects of excessive nutrient loading of waterways.

## 1.1 BACKGROUND

At least three commercial formulations containing ivermectin are available for use in cattle in New Zealand. Of these, the Merial product Ivomec® is not registered for use in lactating cattle. However, Bomactin®, a pour-on product marketed by Bomac, and Iverpor®, marketed by Novartis, are both registered for use in lactating cattle. Also a new product, Eprinex® (eprinomectin), has been produced by Merck and is distributed in New Zealand by Merial. The eprinomectin molecule is structurally very similar to that of ivermectin but is more potent against internal parasites and partitions away from fat, indicating that it is not associated with milk and therefore can be used in lactating cattle. In terms of its potential environmental impact on invertebrates, work by Merck has shown that it has around 10 times less impact than does ivermectin (Barry McPherson, Merial, Auckland, pers. comm.).

This review summarises what is known about the impact of ivermectin in pastures; these environmental effects have been well studied in terms of cowpat deposition in pasture. One of us (SDW) has published the results of a two-year field trial, a mathematical model, a substantial review and a popular article on this topic (Wratten et al. 1993; Wratten & Forbes 1995, 1996; Sherratt et al. 1998). Limited environmental information is available on the effects, if any, of ivermectin in dairy shed effluents.

The major focus of the environmental impact of dairy effluents has typically been the effects of increased nutrient loads, biochemical oxygen demand (BOD), and faecal contamination (Schofield et al. 1990; Foy & Kirk 1995; Havens et al. 1996; Deely et al. 1997; Donnison & Ross 1999; Foy et al. 2001). Far less consideration has been given to the effects of drugs and other chemicals, such as detergents and disinfectants, which are used in the dairy industry (Schindler 1993; Gunn & Sadd 1994). Ivermectin is a drug used for the control of lice and parasitic worms in cattle in New Zealand (P. Bodekker, Dairy Insight, pers. comm.), although, as mentioned above, it is not used in lactating cows. Additionally, quantities of detergents and disinfectants are used in the dairy industry, detergents representing the biggest portion of chemicals used in dairy operations (Schindler 1993). Such detergents and disinfectants may lead to the release of endocrine-disrupting chemicals (EDCs) such as nonylphenol, a persistent byproduct of degradation of the non-ionic surfactants, alkylphenol polyethoxylates.

There is little information on the specific acute and chronic effects of dairy discharges on the environment. It is known that pollution from farm waste has been a principal cause of deterioration in river quality (Foy et al. 2001). It has also been shown that decreases in water and ecosystem qualities are correlated with the stocking rate of grazing animals (Foy & Kirk 1995). Agricultural pollution is also associated with high BOD and low dissolved oxygen. However, how and which farming activities affect the chemical and biological quality of catchments is not well understood (Schofield et al. 1990). The environmental impact of dairy effluents depends on the type and quantity of chemicals used and on the efficiency of wastewater treatment (Schindler 1993). Solving pollution issues related to farming activities in receiving catchments appears to be challenging. For example, in the UK, the introduction of measures to control farm pollution point sources did not result in recovery of stream ecology. This unexpected lack of improvement was explained by the potentially high polluting capacity of short-lived farm pollution incidents (Foy et al. 2001).

## 1.2 OBJECTIVES

To carry out an initial literature search and report on the potential adverse effects on terrestrial and aquatic invertebrates and freshwater fisheries exposed to (a) ivermectin and (b) oestrogens in dairy discharges to land and receiving water-catchments.

# 2. Properties and environmental effects of ivermectin

## 2.1 PROPERTIES AND USAGE

Ivermectin (22,23-dihydroavermectin B<sub>1</sub>) is a broad-spectrum antiparasitic drug that was introduced for the control of ectoparasites and endoparasites of sheep and cattle (Gunn & Sadd 1994). It is a member of a family of compounds, the avermectins, a class of chemicals active against a broad spectrum of nematode and arthropod parasites of animals. Ivermectin is a derivative of avermectin B<sub>1</sub>, a high-molecular-weight fermentation product of microbial cultures of the soil-dwelling actinomycete *Streptomyces avermitilis* (Campbell et al. 1983). Avermectin B<sub>1</sub> acts by blocking signal transmission from interneurons to excitatory motoneurons, specifically that of the gamma-aminobutyric acid (GABA) neurotransmitter (Campbell et al. 1983). In invertebrates such as nematodes and arthropods, GABA-mediated nerves primarily control the peripheral muscles, and administration of ivermectin results in paralysis and death of the parasite either through starvation or detachment from the host (Gunn & Sadd 1994). However, ivermectin is not active against protozoa, flukes, or tapeworms, presumably because neurotransmission in these groups is not GABA-mediated (Campbell et al. 1983). In mammals, GABA-mediated nerves

occur only in the central nervous system and therefore ivermectin should have a limited effect provided it does not cross the blood-brain barrier.

Ivermectin may be administered orally, via subcutaneous injection, or as a pour-on formulation (Bloom & Matheson 1993). In New Zealand, Ivomec® is primarily administered orally, as a drench, to calves at weaning, and then as needed in adult (non-lactating) cattle (P. Bodekker, Dairy Insight, pers. comm.). Bomactin® and Iverpor® are both pour-on formulations.

Concerns over potential environmental side-effects of ivermectin usage exist, as a large percentage of the drug is excreted unmetabolised in faeces of treated animals (Halley et al. 1989; Gunn & Sadd 1994). For example, 39%, 69%, and 43% of the initial doses of radioactive ivermectin were recovered in faecal samples of steer, sheep, and swine treated via subcutaneous or intraruminal injections at levels of 50%, 50%, and 33% above recommended dosages, respectively (Halley et al. 1989). In a worst-case scenario of feedlot waste collected after a 7-day period, the calculated concentration of unmetabolised ivermectin from cattle treated with subcutaneous injections of ivermectin at 200 mg/kg body weight was approximately 351 µg ivermectin/kg faeces wet weight. If this waste was to be used as fertiliser (spread at a rate of 15 ton/acre (5.5 t/ha) and ploughed to a depth of 15 cm), soil concentrations of ivermectin were estimated as 5.1 µg/kg of soil (Bloom & Matheson 1993).

## 2.2 SORPTION AND BIODEGRADATION OF IVERMECTIN

The distribution of ivermectin within the environment will determine the level of exposure to organisms. Ivermectin has a vapour pressure of approximately  $1.5 \times 10^9$  mm Hg, indicating that it is not very volatile and therefore would be unlikely to disperse into the atmosphere (Bloom & Matheson 1993). It has a low solubility in water and a high affinity for organic matter (octanol/water partition coefficient ( $K_{ow}$ ) of 1651, and soil organic carbon distribution coefficient ( $K_{oc}$ ) of 12 600–15 700) and therefore will tend to be strongly sorbed to soil and sediments (Bloom & Matheson 1993). Ivermectin degrades to more polar, less toxic metabolites in the environment. Biodegradation is largely temperature-dependent, with half-lives ranging from 1–2 weeks for soil/manure mixtures in outside summer temperatures to 35 weeks for soil/manure mixtures stored at 22°C in the laboratory and in the dark (Halley et al. 1989). Ivermectin can be photodegraded near the surface of open waterbodies, with half-lives of 12 h in summer and 39 h in winter (Bloom & Matheson 1993).

## 2.3 EFFECTS OF IVERMECTIN ON TERRESTRIAL AND AQUATIC INVERTEBRATES

The toxicity of ivermectin to a selected number of terrestrial and aquatic invertebrates has been assessed in the laboratory. Toxicity to the earthworm *Eisenia foetida* has been determined in two studies. Halley et al. (1989) derived an  $LC_{50}$  of 315 mg/kg while Gunn & Sadd (1994) calculated an  $LC_{50}$  of 15.8 mg/kg

(Table 1). The large discrepancy is likely to be explained by differences in experimental designs: Halley et al. (1989) used pure technical-grade ivermectin and conducted the experiments at a high soil pH, while Gunn & Sadd (1994) used the formulated drug (i.e. ivermectin in the presence of stabilisers, emulsifiers, etc.), which may make it more readily absorbed by the earthworm. The results of Gunn & Sadd (1994) are a more appropriate indication of a real situation where technical grade ivermectin is applied. Gunn & Sadd (1994) found that earthworm growth was affected by ivermectin, with an  $EC_{50}$  of 4.7 mg/kg, and that cocoon production was reduced at concentrations of 4 mg/kg. Concentrations higher than these reported effect-levels have been observed in faeces of cattle 17 days after their treatment with ivermectin drench or injectable ivermectin (Sommer et al. 1992). However, Bloom & Matheson's (1993) estimate of soil ivermectin concentrations following spreading of faecal material from ivermectin-treated cattle as fertiliser is 5.1 µg/kg, which is well below levels that affect earthworms.

Unmetabolised ivermectin in treated animal faeces can affect dung-dwelling invertebrates and insect species under some circumstances (Wall & Strong 1987; Halley et al. 1993; Floate 1998). This biocidal action could be considered beneficial for the control of pest insects such as stable flies and the larvae of animal parasites; however, there is also an effect under some experimental regimes on non-pest invertebrates such as dung beetles (Wall & Strong 1987). The consequent influence of ivermectin on dung decomposition is debated. Some authors, who have shown decreased populations of dung-dwelling invertebrates and insects in the faeces of animals treated with ivermectin, suggest this also reduces the rate of dung decomposition (Wall & Strong 1987; Floate 1998). Similarly Gunn & Sadd (1994) suggest that the impact of ivermectin on the growth and fecundity of earthworms, which are closely associated with cowpats and important to their degradation, may explain the retardation of cowpat decomposition in pastures of ivermectin-treated cattle, as observed by other authors. While an increase in the time for decomposition of dung from treated animals was observed under laboratory conditions, the number of earthworms found in dung pats from control cattle and ivermectin-treated cattle was similar (Halley et al. 1993). These authors suggest that the variety of physical, chemical and biological factors (e.g. weather, climate, soil type, soil fauna) that influence dung decomposition are more significant and that, under field conditions, the presence of ivermectin residues has no significant effect on dung degradation rates (Halley et al. 1993).

Concerns about the effect of ivermectin on dung-nutalising insect populations and the potential for consequent persistence of dung on pastures have been raised. However, Wratten et al. (1993) published the results of a two-year study of the rate of decomposition of cattle dungpats exposed to normal environmental influences. The cattle had been treated at therapeutic levels with either an injectable or a sustained-release bonus formulation of ivermectin. The rate of decomposition of the dungpats, the extent of their avoidance by the cows, the organic matter content of the soil, and the populations of earthworms in the pastures did not differ between treated cattle and controls. The model of Sherratt et al. (1998) was a detailed simulation model which provided estimates of insect mortality in cattle farms under realistic sets of assumptions. The impact of avermectins on dung insect populations was highly dependent on a



TABLE 1. LABORATORY TOXICITY OF IVERMECTIN TO INVERTEBRATES.

| SPECIES  | DURATION OF TEST | LC/EC <sub>50</sub>   | REFERENCE          |
|--|------------------|-----------------------|--------------------|
| <i>Daphnia magna</i><br>(water flea)             | 48 h             | 0.025 mg/L            | Halley et al. 1989 |
| <i>Crassostrea virginica</i><br>(eastern oyster) | 96 h             | 430 µg/L              | Davies et al. 1997 |
| <i>Panaeus duorarum</i><br>(pink shrimp)         | 96 h             | 1.6 µg/L              | Davies et al. 1997 |
| <i>Eisenia foetida</i><br>(earthworm)            | 28 d             | 315 mg/kg soil        | Halley et al. 1989 |
|  | 14 d             | 15.7 mg/kg soil       | Gunn & Sadd 1994   |
| <i>Arenicola marina</i><br>(marine annelid)      | 10 d             | 0.0238 mg/kg sediment | Davies et al. 1998 |
| <i>Corophium volutator</i><br>(amphipod)         | 10 d             | 0.18 mg/kg sediment   | Davies et al. 1998 |
| <i>Asterias rubens</i><br>(starfish)             | 10 d             | 23.6 mg/kg sediment   | Davies et al. 1998 |

range of environmental factors, and it was concluded that in typical farming systems the maximum cumulative insect mortality in a given season was unlikely to be greater than 25%. A wider analysis carried out by Wratten & Forbes (1996) in a major review of the literature concluded that even under conditions of relatively high levels of avermectin use in cattle, the impact on non-target insect populations and their ecological function is limited.

The water flea (*Daphnia magna*) is the most sensitive freshwater invertebrate crustacean species tested in the laboratory (Table 1). However, ivermectin has a low solubility in water and a high affinity for organic matter and, in the presence of sediment and/or suspended solids, toxicity is significantly reduced. The marine annelid worm, *Arenicola marina*, was the most sensitive sediment-dwelling species tested (Table 1). Ivermectin is also used to control sea lice in farmed salmon, and the predicted environmental concentration of ivermectin in marine sediment around a salmon farm was estimated at 33.4 µg/kg, with a half-life greater than 100 days (Davies et al. 1998). These authors concluded that there might be a significant risk to some sediment-dwelling species around the cages of farmed salmon treated with ivermectin. This was further confirmed by scientists in the UK, who concluded that ivermectin had the potential to affect the European marine environment (Codling et al. 1998).

## 2.4 EFFECTS OF IVERMECTIN ON FRESHWATER FISHERIES

Fish are approximately 100 times less sensitive to ivermectin than *Daphnia magna* (Table 2), with bluegill sunfish and rainbow trout showing 96-h LC<sub>50</sub> values of 5.3 and 3.3 µg/L, respectively (Bloom & Matheson 1993). In addition, ivermectin was shown to be rapidly depurated from bluegill sunfish and to not accumulate in fish (Halley et al. 1993). Beyond these laboratory tests, there is nothing published on the effects of ivermectin in freshwater systems.

TABLE 2. TOXICITY OF IVERMECTIN TO AQUATIC ORGANISMS.

| SPECIES  | DURATION OF TEST | LC/EC <sub>50</sub> | REFERENCE          |
|--|------------------|---------------------|--------------------|
| <i>Daphnia magna</i><br>(water flea)             | 48 h             | 0.025 mg/L          | Halley et al. 1989 |
| <i>Neomysis integer</i><br>(mysid shrimp)        | 96 h             | 0.07 µg/L           | Davies et al. 1997 |
| <i>Salmo gairdneri</i><br>(rainbow trout)        | 96 h             | 3 µg/L              | Halley et al. 1989 |
| <i>Lepomis macrochirus</i><br>(bluegill sunfish) | 96 h             | 4.8 µg/L            | Halley et al. 1989 |
| <i>Mytilus edulis</i><br>(mussel)                | 96 h             | 400 µg/L            | Davies et al. 1997 |

### 3. Oestrogens and other components of dairy discharges

There is little information related to the presence of compounds with oestrogenic activities or other types of endocrine-disrupting chemicals (EDCs) in wastewater from dairy operations. A wide variety of chemicals is used in the dairy industry, including detergents and disinfectants, and the non-ionic surfactants in such detergents can have oestrogenic activities (Schindler 1993). The presence of oestrogenic chemicals in dairy shed effluents should be addressed, particularly with regards to large dairy operations, which can place extremely heavy burdens on receiving river-catchments.

### 4. Conclusions and recommendations

A brief overview has been presented on the environmental effects of contaminants in dairy effluent that may cause environmental harm and/or endocrine disruption. The New Zealand Ministry for the Environment recognised that the conversion of land to dairy operations is likely to increase pollutant pressure on freshwater systems in rural New Zealand and particularly in the South Island ([www.mfe.govt.nz/about/Chapter\\_3.pdf](http://www.mfe.govt.nz/about/Chapter_3.pdf)). The main conclusions of this Ministry for the Environment report are:

- Pollutants originating from dairy shed operations include not only animal waste and nutrients, but also veterinary drugs and other chemicals used daily, such as detergents and disinfectants.

- Ivermectin could occur as a direct consequence of dairy shed operations. Its effects could occur at the paddock level but, as stated above, these are likely to be minor in ecological terms. In freshwater ecosystems, virtually nothing is known. However, Davies et al. (1998) suggested that there might be a significant risk to organisms living in the sediment below farmed salmon treated with ivermectin, but there was no field evidence for this.
- It is possible that ivermectin and EDCs with oestrogenic activity can occur in dairy shed effluents, and their presence should be monitored and the risk of adverse impacts on the environment established.

No New Zealand-based literature on the monitoring of chemicals from dairy discharges could be found. Therefore it is recommended that a more in-depth review of international and New Zealand information on dairy discharges and other relevant agricultural effluents toxicities should be conducted. For example, regional councils could be approached to determine whether unpublished databases on the impact of dairy effluents exist in New Zealand.

Monitoring of dairy shed discharges should include chemical residue analyses for chemicals of potential concern such as some drugs and some EDCs with oestrogenic activity. The use of effect-based screening methods would contribute useful information.

The relative risk of chemical contaminants from dairy discharges should be evaluated as part of a holistic assessment, which would include other issues such as coliform and nutrient loads.

Finally, a survey of the extensiveness of the use of ivermectin-containing drugs in dairy sheds in New Zealand could be useful.

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